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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,029	03/16/2001	Martin C. Barnardo	1181-251	5589

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/809,029	**Applicant(s)** BARNARDO ET AL.	
	Examiner Gary W. Counts	**Art Unit** 1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 May 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *NONE*.
   Claim(s) objected to: *NONE*.
   Claim(s) rejected: *1-7, 9-17, 20, 22-28*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see continuation sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

LONG V. LE 05/12/06
SUPERVISORY PATENT EXAMINER
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Attachment to Advisory Action

Continuation of 11 NOTE: Applicant argues that the instant invention is drawn to methods of detecting anti MHC antibodies but is not directed to the recombinant MHC molecules themselves. This is not found persuasive because as stated in the final action filed 03/03/06 a disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product. In the instant invention given that the recombinant MHC molecule which presents a unique epitope of a naturally occurring MHC allele and binds to only one allele specific anti-MHC antibody is critical to the invention and as stated in the prior Office action Applicant has not adequately described the recombinant MHC molecules, thus the Applicant does not satisfy the requirements of 35 USC 112, first paragraph drawn to written description.

Applicant argues that the protein molecules were unknown in the cited cases (*Lily, Enzo)* and that the instant invention is not directed to unknown proteins. Applicant states that the cases upon which the Office Action relies are inapplicable to the pending application. Applicant points to *Amgen Inc. v. Hoechst Marion Roussel, Inc.,* where the cells were known and methods of using the cells are known. This is not found persuasive because Amgen is not on point. The arguments have been considered but have not been found persuasive because Applicant has not demonstrated a nexus between the fact pattern in the instant specification and that in *Amgen Inc. v. Hoechste Marion Roussel, Inc.* Although Applicant points to the statement that the claims at issue were directed to types of cells that could be used to produce human EPO, and the court stated that "[the] Eli Lilly [decision]...[is] inapposite to this case because the claim terms

at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend.". This is not found persuasive because unlike the known cells of *Amgen,* structure of the broadly claimed recombinant MHC molecules is unknown because no complete structure is known nor any physical or chemical characteristics of the recombinant MHC molecule, nor any physical or chemical characteristics of the recombinant MHC molecule nor any functional characteristics coupled with a known or disclosed correlation between structure and function for the binding of allele specific anti-MHC antibodies which bind to a recombinant MHC molecule that presents a unique epitope of a naturally occurring MHC allele and binds to only one allele specific anti-MHC antibody. Similar to the Lily case, the broadly claimed, unknown structures are critical to the instant invention. Thus the citation, by Examiner of Lilly is appropriate.

Applicant directs Examiner's attention to *Capon et al., v. Eshhar et al. v. Dudas.* which Applicant states that Capone utilizes known biological materials and thus is relevant to the instant rejection. Applicant summarizes the relevant sections of *Capon v. Eshhar* wherein Applicant states that the Federal Circuit elaborated that "[t]he Board's rules that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization." Applicant states that the Federal Circuit made this assertion that nucleotide sequences need not be fully presented to satisfy the written description requirement, because the sequences of a sufficient number of sequences of the DNA chimera components were available in the published literature and methods

were known and provided for linking the components of the chimera. This is not found persuasive because the instantly claimed invention is not drawn to sequences or protein molecules that are known in the prior art, but rather are drawn to the use of recombinant MHC molecules that are structurally undefined comprising structurally undefined epitopes and therefore the findings in *Capon v. Eshhar* are not relevant to the instant rejection. Applicant also points to Table 4, which lists multiple alleles of HLA (MHC) and their loci and also points to websites that depict the coding sequences of MHC molecules. This is not found persuasive because Applicant is arguing limitations that are not recited in the claims. The claims are directed toward recombinant MHC molecules not naturally occurring MHC molecules. Therefore, since the use of recombinant MHC molecules that presents a unique epitope of a naturally occurring MHC allele are critical for detecting anti-MHC molecules and since the specification does not describe the recombinant MHC molecules, the specification thus fails to describe the claimed methods.

Applicant argues that the Office Action's reliance on paragraph 0026 is misplaced and taken out of context, because the cited passage in the Office Action describes "functionally equivalent variants, derivative or fragments" of MHC molecules. This is not found persuasive because the claims recite "one or more recombinant MHC molecules which contains one or more epitopes of said naturally occurring MHC allele", and the claims recite open language i.e comprising. Therefore, the recombinant molecule does not exclude additions or deletions to the one or more epitopes as recited and as shown by Applicant on page 8, lines 18-34 as will be appreciated the maintenance of not only

residues at the epitopic site, but also key skeletal residues to achieve correct folding of the MHC molecule to form the epitopic site must be considered.

Applicant argues that paragraph 0075 of currently pending published application outlines a strategy for preparing recombinant HLA molecules and also includes examples to make and use MA-A11 and MA-B7, as well as those recombinant MHC molecules that the Office Action indicates are enabled (HLA-A2 and HLA-B8) (it is noted that MA-A11 and MA-B7 appear to be typographical errors in the patent application publication 2003/0017447, a review of the specification which was filed 03/16/01 on page 22, line 32 indicates HLA-11 and HLA-B7). This is not found persuasive because as stated in the previous Office Action the specification does not teach any and all recombinant MHC molecules that will function as claimed. The identification of these recombinant MHC molecules do not predictably enable the broadly claimed invention because other than this teaching, the specification provides no information as to structures common to the any and all recombinant MHC molecules that allow one of skill to predictably make the claimed recombinant MHC molecules based on a structure/function correlation. Applicant argues that given the state of the art the specification is replete with alleles that can be used to generate recombinant MHC molecules (Applicant directs Examiner's attention to Table 4). This is not found persuasive because of reasons stated above and because the structure of the recombinant MHC molecule is unknown and also as disclosed in the specification it was surprisingly found that individual recombinant HLA molecules could be used for specifically detecting anti-HLA antibodies. Further, the example in which Applicant

refers to make recombinant molecules was also found to be surprising. Page 12, line 27 – page 13, line 3 discloses that the recombinant MHC is synthesized in a prokaryotic expression system (see Example 1). It will therefore be understood by those skilled in the art that the MHC molecule will be synthesized in an un-glycosylated form, as prokaryotic cells do not have the capacity to glycosylate proteins. Glycosylated sites are known to play important roles in ligand binding, and would therefore be thought to be a necessary component of anti-MHC antibody binding to MHC molecules. Surprisingly, the inventors have discovered that the lack of glycosylation of the recombinant HLA or HLA-type molecules is not detrimental to anti-HLA antibody binding. Thus, it would be surprising that this would occur in any and all recombinant molecules.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary Counts
Examiner
Art Unit 1641
May 18, 2006